REMARKS

The Examiner is thanked for the due consideration given the application. A Declaration is attached to this paper.

Claims 28, 31-34, 37, 38 and 40-67 are pending in the application. Rejoinder is noted with appreciation. Claims 30, 62 and 63 have been canceled by this amendment. Independent claim 28 has been amended to add a step of selecting from among the enumerated agents, including 4-OH-OPB and set forth specific stimulation of clonal growth in ***sparsely*** distributed cells (see page 4, line 14 of the specification). Claim 51 ha been amended to remove reference to p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4-hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof. Other amendments to claim 28 find support at page 40 of the specification. Independent claim 61 has been amended to set forth a simplified method including selecting a specific clonal inhibitor or 4-OH-OPB. New claims 65-70 set forth a method for preparing a pharmaceutical preparation.

No new matter is believed to be added to the application by this amendment.

Statement of Substance of Interview

The Examiner is thanked for graciously conducting an interview with the Applicant's representative on January 19, 2011. During the interview potential claim amendments were discussed in regards to the types of agents being more explicit

(including 4-OH-OPB) and a sequential limitation for stimulation of clonal growth "*in sparsely distributed cells*". These potential claim amendments were discussed in light of the Howell et al. reference (U.S. Patent 5,597,798), which does not disclose 4-OH-OPB.

At the end of the interview the Examiner prepared an interview summary. The interview summary has been reviewed and it appears to accurately reflect the substance of the interview.

Claim Objections

Claim 30 has been objected to as further limiting the subject matter of a previous claim. Claim 30 has been canceled by this amendment, thereby rendering this issue moot.

Rejections Under 356 USC §112, First Paragraph

Claims 51-53, 55 and 60 were rejected under 35 USC §112, first paragraph as not being enabled. This rejection is respectfully traversed. Claims 28, 30-34, 37, 38, 40-61 and 63 were rejected (old and new rejections) under 35 USC §112, first paragraph as not complying with the written description requirement.

These rejections are respectfully traversed.

The Office Action asserts that that some agents are enabled and described and some do not, including p-hydroxy-azobenzene, 2-Butyl-2-hydroxy-N-(4-hydroxy-phenyl)-N'-phenyl malonamide, 1,2-diphenyl-4-hydroxy-4-[2-(phenylsulfinyl)ethyl]-3,5-pyrazolidinedione, and analogues thereof (such as 4-OH-OPB).

Although the point is not conceded, these recitations have been removed from the claims without prejudice in order to prosecute prosecution on the merits.

Regarding the rejections of claims 54-56 (pertaining to HIV and anti-viral treatment), support can be found at paragraphs [0226], [0242] and [0298] of corresponding publication US 2006/0121449 A1 as well as, e.g., in Example 11a, which pertains to HSV.

Regarding the "seeding" limitation discussed at page 34 of the Office Action, claims 28 and 61 have been amended to better correspond to the support found at page 40 of the specification or to remove this limitation.

These rejections are believed to be overcome, and withdrawal thereof is respectfully requested.

Rejection Under 35 USC §112, Second Paragraph

Claims 60 and 63 were rejected under 35 USC §112, second paragraph as being indefinite. This rejection is respectfully traversed.

The comments in the Office Action have been considered, and the claims have been amended to remove reference to Mito+, potential drugs and potential toxins.

Any issues pertaining to claim 63 are mooted by the cancellation of that claim. However, it is believed that no broad/narrow range limitations are set forth in the claims but rather permissible alternative recitations.

This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

Art Rejections

Claims 47-54, 56, 57, 59 and 60 remain rejected under 35 USC §102(b) as being anticipated by WO 01/00585 (TJOTTA et al.) as evidenced by SZUCS et al. (*Bulletin WHO* 1988 66: 729-737).

Claims 47-53, 56, 57, 59 and 60 remain rejected under 35 USC §102(b) as being anticipated by GERNER et al. (U.S. Patent 6,258,845).

Claims 47-53, 56, 57, 59 and 60 remain rejected under 35 USC §102(b) as being anticipated by HAYASHI et al. (U.S. Patent 4,880,742) as evidenced by McCLAIN et al. (*FASEB Journal*, 1995 9: 1345-1354).

Claims 47, 48, 59 and 60 remain rejected under 35 USC §102(b) as being anticipated by DE ASUA et al. (of record).

Claims 47, 48, 59 and 60 remain rejected under 35 USC §102(b) as being anticipated by KAMEI (of record).

Claim 58 remains rejected under 35 USC §103(a) as being unpatentable over TJOTTA in view of TANNOCK (*Experimental Chemotherapy*).

Claims 28, 30, 31, 34, 38, 40, 41, 42, 43, 44, 46, 47, 50-53 and 59-63 were newly rejected under 35 USC §102(b) as being anticipated by HOWELL et al. (U.S. Patent 5,597,798) as evidenced

by YourDictionary.com in view of BAGASRA et al. (Cancer Immunol. Immunotherap. 1985 20:55-600).

Claim 33 was newly rejected under 35 USC §103(a) as being unpatentable over HOWELL et al. in view of BAGASRA et al., De ASUA et al. and KAMEI.

Claim 37 was newly rejected under 35 USC §103(a) as being unpatentable over HOWELL et al. in view of BAGASRA et al. and TAMI et al.

Claim 45 was newly rejected under 35 USC §103(a) as being unpatentable over HOWELL et al. in view of BAGASRA et al. and LIM et al. (Jpn. 1. Cancer Res. 93: 36-41, Jan. 2002).

Claims 28, 30-32, 34-36, 38-41, 43, 44, 46, 47, 50-53, 59 and 60-63 were newly rejected under 35 USC §103(a) as being unpatentable over PRECHEL et al. (*Cancer Letters*, 1995,92: 235:242, of record) as evidenced by CAR et al. (*Toxicologic Pathology*, 1999, Vol. 24:58-63, of record) in view of BAGASRA et al.

These rejections are respectfully traversed.

Distinctions of the present invention over the previously applied art have been made of record in the application which, for brevity, are not repeated here.

The present invention is directed at the utilization of 4-OH-OPB or its analogues for the treatment of diseases such as cancer. This can include:

• a) Inhibition or stopping development of metastases of local infiltration. Malignant diseases derived from T4 lymphocytes or Kaposi's sarcoma are not included.

• b) When using conventional chemotherapy, simultaneous use of 4-OH-OPB is expected to prolong the period of the effect of such chemotherapy since resistant tumor clones are not allowed to develop (see experiment 16).

4-OH-OPB and its analogues can be used for the treatment of HIV:

• a) New infections before development of congestion of cells infected with defect HIV that is unable to destruct the host cell.

• b) Older HIV infections or AIDS where the congestion of the cells containing defect virus has become too big. The effect of 4-OH-OPB is then suspended. In order to get 4-OH-OPB working again, the congestion of cells with defect HIV need to be drastically reduced.

4-OH-OPB and its analogues can be used for the treatment of psoriasis or treatment and prophylaxis of arteriosclerosis:

• a) Compounds that inhibit specific clonal growth of sparsely seeded cells, but not identical cells in the same culture that were collocated.

• b) Compounds that stimulate specific clonal growth of sparsely seeded cells, but not identical cells in the same culture that were collocated.

Compounds in contact with the body, inside or outside, should be tested along these lines since there are indications that compounds mentioned under a) will prolong life when reducing cancer or arteriosclerosis. Those under b) will probably behave in reverse order and increase the probability of contracting cancer or arteriosclerotic complications. Therefore, both of these aspects are important for public health.

Independent claim 28 has been amended to add an additional step: "*a) selecting an agent selected from the group consisting of 4-OH-OPB, drugs, food, food additives, toxins, and microbes, or components from physiological or pathological processes, where said agents or components demonstrate specific inhibition or specific stimulation of clonal growth in only* ***sparsely*** *distributed cells, not in collocated areas of identical cells.*"

It is respectfully submitted that the applied art alone or in combination does not anticipate or render unpatentable independent claims 28 and 61 of the present invention.

Particularly HOWELL et al. do not disclose or infer the use of 4-OH-OPB and do not seed their cells sparsely as in the sense of the present invention where a cell density gradient in

agar culture made it possible to compare the effect on both sparsely and densely distributed cells in the same culture.

Moreover, the inventor of the present invention, Dr Tjøtta, has studied the applied art and wishes to submit the following observations.

The invention of HOWELL et al. sets forth a method of sensitizing various types of cancer cells derived from different tissues of origin to various cytotoxic agents and augmenting the sensitivity of cancer cells to these cytotoxic agents. The invention provides a method to treat cancer and other cell proliferative diseases by the administration of a sensitizing agent prior to or concurrently with the administration of a cytotoxic agent.

This is not the aim of my patent application:

1. Cytotoxic agents are not examined or included in any claim.

2. Only compounds that inhibit or stimulate growth of cells (normal, transformed (experiment no. 5)), cancer cells (experiment no. 7-9) or immune cells (experiment no. 10) that are seeded sparsely in soft agar (experiment no. 5) or that are mixed with other cells of other specificities (as the immune cells of the spleen (experiment no. 10)) or cells going to develop cancer (see last paragraph on page 42 and first paragraph on page 43) or cells going to spread from a malignant tumor in an individual (experiment no. 9) are included.

Technically HOWELL et al. seed their cells sparsely at about 4000 cells in one ml in dishes of 3.5 cm in diameter, ***but they did not compare the effect of the studied compounds on sparsely seeded cells with the effect in collocated areas of identical cells***. In my experiments, however, often between 35000 and 144000 cells were seeded in wells of 15 mm in diameter in 0.3 ml top soft agar layer on a bottom agar layer of 0.3 ml.

The top layer containing the cells was placed on a bottom layer cast at an oblique angle of about 12 degrees in order to create a cell density gradient in the top layer.

The cell gradient on the side of the well with the minimal cell number contained only about ¼ of the total cell number of the well. However, the most sparsely distributed cell area on the same side of the well only contained very few cells.

This gradient made it possible to compare the effect on cell growth induced by a compound on both sparse and crowded areas in the same well. I only looked for compounds with specific inhibition or stimulation only on cells that were sparsely seeded and not on collocated identical cells.

In addition I cannot find HOWELL et al. using 4-OH-OPB, the definitely best compound detected by the method described in my invention (published as WO 2004/055175 A1). 4-OH-OPB was the only compound among the studied ones that was able to rescue mice transplanted with Ehrlich carcinoma and completely stop the development of metastases (experiment no. 7-9). However, if the

transplantable Ehrlich cancer developed tumors, 4-OH-OPB had no inhibiting effect on their growth (experiment no. 9).

There are no indications either that 4-OH-OPB may be a sensitizing agent as described by Howell et al.

Cytotoxic agents are mentioned by me in connection with a quite different field. Since 4-OH-OPB stops the development of new clones (experiment no. 13), also tumor clones resistant to cytotoxic agents are expected to be included. Therefore, the effect of treatment with cytotoxic agents also is expected to last longer before losing activity against a malignant disease if 4-OH-OPB is given simultaneously.

These observations are being resubmitted in the form of a Declaration.

This in light of the traversal of record therefore demonstrate that not only anticipation or *prima facie* unpatentability has been demonstrated, but that the present invention yield unexpected results that would fully rebut any unpatentability that could be alleged.

These rejections are believed to be overcome and withdrawal thereof is respectfully requested.

The fee of $104 for the four claims of any type being added herewith, is being paid concurrently online by credit card.

Conclusion

New claims 64-70 have been newly presented for consideration on the merits. It is believed that new claims 64-70 are instantly patentable for at least the above reasons.

The rejections are believed to have been overcome, obviated or rendered moot and no issues remain. The Examiner is accordingly respectfully requested to place the application in condition for allowance and to issue a Notice of Allowability.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

/Robert E. Goozner/
Robert E. Goozner, Reg. No. 42,593
209 Madison Street, Suite 500
Alexandria, VA 22314
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

REG/fb